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13. ABSTRACT (Maximum 200 words)

Several lines of evidence support a "parallel processing" view for short- and long-term memory in *Aplysia*: (1) The cellular analog of long-term memory, long-term synaptic facilitation (LTF), can be induced by repeated applications of the neuromodulator serotonin (5HT) in the complete absence of the analog of short-term memory, short-term facilitation (STF). (2) STF and LTF can be dissociated by their temporal dynamics: STF decays within 2 hours, whereas LTF does not begin to be expressed until 10-15 hours. (3) A novel stage of intermediate-term facilitation (ITF) seems to be a precondition to triggering the long-term process (LTF). (4) It has long been known that spaced behavioral training typically produces superior memory compared to massed training. We observe a related phonemenon at the synaptic level: 5 spaced applications of 5HT induces STF, ITF and LTF, whereas comparable exposure to 5HT at one time induces only STF and ITF; no LTF is induced. Finally, at a behavioral level, we find that long-term memory for sensitization can be induced in the absence of short-term memory.

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1. **COVER SHEET**

FINAL TECHNICAL REPORT

Air Force Office of Scientific Research

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2. OBJECTIVES:

The primary objective of this project was to carry out a mechanistic analysis of the relationship between short-term and long-term information processing in central neural circuits of *Aplysia*.

3. SUMMARY OF ACCOMPLISHMENTS

The information processing that we examined falls into two broad classes, one involving facilitation; the other inhibition. I will discuss each in turn.

A. *Facilitatory Processing*

The facilitatory processing we have examined takes place at identified sensory-motor synapses in the tail-elicited siphon withdrawal reflex. Behaviorally, a single tail shock induces short-term memory for sensitization in this reflex, whereas 5 repeated shocks induces long-term memory. These effects can be duplicated at a cellular level: a single pulse of the neuromodulator serotonin (5HT) induces short-term facilitation (STF) whereas 5 pulses induce long-term facilitation (LTF). We have found that these two processes can be dissociated in a variety of independent ways, supporting the general hypothesis that important features of short-term and long-term memory in *Aplysia* may be processed independently and in parallel. First, LTF can be induced in the complete absence of STF. This can be accomplished either by exposing only the sensory neuron cell body to 5HT, or by low concentrations of 5HT; in either case no STF is induced, but STF is expressed 24 hours later. Second, STF and LTF can be dissociated by their temporal dynamics: STF decays within 2 hours, whereas LTF does not begin to be expressed until 10-15 hours. Third, we have identified a novel stage of facilitation by systematically varying 5HT exposure: 1-4 pulses gives rise to a rapidly decaying STF (within 15 min) while 5 pulses trigger an intermediate term facilitation (ITF) which lasts at least 90 min. Interestingly, the expression of ITF seems to be a pre-requisite for the induction of LTF. Fourth, behavioral experiments in many experimental systems show that distributed (spaced) training typically produces superior memory compared to masses training. We have discovered a related effect at the synaptic level: 5 spaced applications of 5HT induce STF, ITF and LTF. However, a single prolonged exposure of 5HT (equivalent to the net exposure with 5 spaced pulses) induces only STF and ITF; no LTF is induced. Finally, in behavioral experiments, using our cellular results as a predictor, we found that long-term memory for sensitzation in the tail induced siphon withdrawal reflex can be induced in the absence of short-term memory. Taken collectively, the results support the view that important aspects of short-term and long-term facilitatory information processing can be induced and expressed in parallel in neural circuits in*Aplysia* neurons.

B. *Inhibitory Processing*

The inhibitory processing that we have examined occurs within the siphon withdrawal reflex (SWR). Work derived from this project has shown that the SWR undergoes activity-dependent gain regulation in response to ambient tactile stimulation. Specifically, weak tactile stimulation of the tail induces transient inhibition in the SWR. STF exhibited by a class of identified inhibitory interneurons (L30s) has been shown to play an important role in this form of modulation. Within the SWR circuit, the L30s provide direct recurent inhibition to the L29s, a class of excitatory interneurons which provides strong synaptic input to siphon motor neurons. Multiple lines of evidence show that enhanced inhibition of the L29s through STF at the L30 synapse underlies reflex modulation in response to tactile stimulation. First, in experiments using reduced behavioral/cellular preparations, we found that the L30s are strongly activated by weak tactile stimulation of the tail, which results in STF at L30 synapses with a time course of approximately 60 seconds. Second, this same tactile stimulation also produces a transient reduction of both siphon-evoked L29 responses and motor neuron responses, each with a time course matching L30 STF. Third, comparable results were obtained using intact, freely-moving animals. Fourth, the L30s were directly implicated in this form of reflex inhibition by reversibly removing 2 (of the 3) L30s from the reflex circuit (by hyperpolarization) during tactile stimulation of the tail; this inactivation of L30s significantly attenuated the inhibition of the reflex. Finally, different components of STF in the L30s appear to be selectively reduced by tail shock. This same tail-shock stimulus also reduces L30-mediated inhibition of the SWR, at both cellular and behavioral levels. Taken together, these data illustrate that STF at the L30 inhibitory interneurons appears to be an intrinsic mechanism for the dynamic regulation of a reflex in response to tactile input, which in turn can provide for rapid on-line gain adjustment during changes in the ambient tactile environment.

4. PUBLICATIONS RESULTING FROM THE PROJECT

A. *Original Publications*

Blazis, D.E.J., Fischer, T.M. and Carew, T.J. (1993) A neural network model of inhibitory information processing in *Aplysia, Neural Computation*. **5**, 213-227.

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B. ***Book Chapters and Reviews***

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Carew, T.J. (1996). Molecular enhancement of memory formation. *Neuron*, **16**, 5-8.

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Fischer, T.M. and Carew, T.J. (1993) L30 interneurons mediate inhibition produced by a weak tail stimulus in the siphon withdrawal circuit of *Aplysia*. *Soc. Neurosci.* **19**, 17.

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